Chapter 6

Favorable Effect of Very Early Disease-Modifying Antirheumatic Drug Treatment on Radiographic Progression in Early Inflammatory Arthritis. The ESPOIR Cohort Study

Published in Lukas C, Combe B, Ravaud P, Sibilia J, Landewé R, van der Heijde D.

Arthritis Rheum 2011;63(7):1804-11

ABSTRACT

Objective: While there is consensus that treatment with disease-modifying anti-rheumatic drugs (DMARDs) should be started early in patients with inflammatory arthritis, confirmation that radiographic progression is inhibited with early treatment start is scarce. This study was undertaken to compare radiographic progression in patients treated with a DMARD very early in the course of their disease (within 3 months of diagnosis) and those who began DMARD treatment later.

Methods: Patients included in the French observational ESPOIR cohort were followed up, and radiographic progression after 12 months was assessed. Propensity scores, reflecting the indication to start a DMARD, were obtained by modeling the start of DMARD therapy by disease-specific and demographic variables obtained at baseline, using logistic regression analysis. The influence of very early versus delayed DMARD start on radiographic progression was evaluated by generalized linear regression, with and without adjustment for propensity scores.

Results: Six hundred sixty-one patients were analyzed. In an unadjusted analysis, patients starting DMARD therapy within 3 months of diagnosis did not show a significant difference in radiographic progression score as compared to those starting DMARD therapy later (1.2 units versus 1.6 units; p=0.37). Adjustment for the propensity score revealed a statistically significant difference in mean progression (0.8 units versus 1.7 units; p=0.033). Analysis by propensity score quintile showed a trend suggesting that early treatment was especially beneficial for patients in the fourth and fifth quintiles (worse prognosis).

Conclusion: Our findings indicate that among patients with inflammatory arthritis in daily clinical practice, early initiation of DMARD therapy reduces 12-month radiographic progression. This strengthens the current recommendations for very early initiation of specific therapy in patients with early arthritis.

INTRODUCTION

A more intensive treatment approach to the management of early inflammatory arthritis has been adopted recently, with a general consensus that a disease-modifying antirheumatic drug (DMARD) with proven structural efficacy should be started as soon as possible in a patient likely to develop persistent and erosive arthritis [1-4]. If classical rheumatoid arthritis (RA) with unfavorable prognostic factors is found at presentation, such a recommendation is obvious, but if a patient is referred very early, a diagnosis and prognostic profile can often not be made. While robust and consistent data has demonstrated both clinical and radiographic superiority of intensive treatment (e.g. DMARD combination therapy), data about the impact of the delay between disease onset and DMARD treatment start remains inconclusive. Current evidence that an earlier treatment start results in a better radiographic outcome in patients with RA is still sparse. Clinical trials have thus far mainly included patients fulfilling the criteria for RA, and these studies show that in early RA intensive therapy is more efficacious than conventional treatment [5-8]. Though, such studies do not prove that an early treatment start is better than a delayed one. The data that suggest a benefit of an early treatment start are often suffering from confounding by indication: Physicians base their treatment decisions on the activity and (thus) severity of the disease. Confounding by indication may lead to a decreased treatment contrast [9, 10]. In the study by van der Heide et al, for example, earlier treatment of patients with recently diagnosed RA resulted in improved clinical outcomes after 12 months of follow-up, whilst no radiographic benefit could be observed, probably because of the tendency of the investigators to use more intensive additional treatment in patients with more severe or persistently active disease [11]. The ideal experiment to investigate whether an early DMARD start is better than a delayed one is a pragmatic RCT in which patients are randomized to an arm with an immediate DMARD start versus an arm with a delayed DMARD start. However, such a study seems to be unethical in light of current treatment algorithms.

Another concern is that no-one can exactly define how early is early enough. A current view, also reflected in new treatment recommendations, exploits the window of opportunity principle as a guidance principle, and many think that 3 months is the maximally allowable delay to start a DMARD after diagnosis [1, 12]. However, such thoughts are based on experts' opinion rather than on scientific data, or were formulated before methotrexate was commonly used as first-line therapy [13].

Among patients with early inflammatory arthritis in the French ESPOIR cohort, there has been variation in the amount of time since onset at which rheumatologists did have first prescribed DMARD therapy. This may theoretically lead to differences in outcome in these patients, which could be clinically meaningful. In the present study we evaluated the impact of the time lag between arthritis onset (first patient-reported swollen joint) and DMARD initiation on 1-year radiographic progression, adjusting for the spurious effects of confounding by indication.

METHODS

Patients. The ESPOIR cohort.

The ESPOIR cohort [14, 15] is a French prospective observational study of adults aged 18 to 70 years recruited from multiple regions across France under auspices of the French Society of Rheumatology. Included patients had to present with inflammatory arthritis lasting for 6 weeks up to 6 months, involving more than 2 joints and diagnosed by the referring physician as RA or RA-like (i.e. a high suspicion of RA). Patients had never undergone treatment with a DMARD or steroids before. Patients were excluded if the referring physician had judged they had other clearly defined inflammatory rheumatic diseases.

Patients were recruited from general practitioners and rheumatologists from 14 regions across France. Data were collected by the regional university rheumatology department, which did not interfere with patient's treatment. Patients were routinely treated and followed up by private rheumatologists in the geographical area, and in exceptional cases by GPs with a special interest in rheumatology.

The results of each test performed for study purposes were periodically communicated to the practitioner taking care of the patient. All patients were followed up by the same investigator every 6 months during the first 2 years and every year thereafter. Data concerning medical history, socio-economic and demographic characteristics, clinical-, biological-, radiographic- and genetic parameters were also collected. One biological resources centre (Paris-Bichat) was in charge of centralising and managing biological data collection.

The first patients were enrolled in December 2002, and in total 813 patients were included.

Radiographic evaluation

Baseline and 1-year radiographs of hands, wrists and feet from included patients were read according to Sharp van der Heijde score, blinded to patient identity, patient characteristics and treatment, but with known time order for reasons of sensitivity to change [16]. In order to evaluate the reproducibility of the radiographic scoring, a set of 30 patients representing the entire range of status- and change scores that was observed during the first read was selected and scored again by the same reader. Intraclass correlation coefficients were calculated for status (baseline and 1 year)- as well as change scores, and the smallest detectable change was computed using standard methodology [17].

Propensity analysis-principles

It is reasonable to assume that in convenience cohorts such as the ESPOIR cohort, without fixed treatment protocol, the most important determinant of an immediate DMARD start is the physician's consideration about the severity and activity of the disease as well as the individual prognosis. Severity and activity of the disease may confound the relationship between time-to-DMARD start and radiographic progression (confounding by indication). However, the physician's interpretation of disease severity and activity is by definition unquantifiable, since it encompasses a number of intangible and often unmeasured factors.

The theory underlying propensity modeling assumes that the likelihood of (in this case) a DMARD start, and thus severity of RA in the opinion of the physician, can be approximated by taking into consideration all measured variables at baseline that the physician may or may not implicitly use to base his or her decision to initiate DMARD treatment (18). By adjusting the relationship between the time to DMARD start and radiographic progression for individual propensity scores, one can partially adjust for confounding by indication.

For each patient, propensity to start DMARD treatment within the 6 months after the first reported synovitis was estimated by logistic regression analysis, modeling all available variables at baseline that, in the opinion of the investigators, could have influenced the decision by the treating physician to prescribe the DMARD. DMARD starts taken into account were starts with DMARDs of proven efficacy in radiographic

progression, i.e., methotrexate, leflunomide, sulfasalazine, and tumor necrosis factor (TNF) blockers (or combinations of these).

This logistic regression analysis resulted in a propensity score for each patient for starting treatment within 6 months, which was the time frame within

which most patients prescribed treatment had actually started this treatment. According to propensity modeling theory, in patients with similar propensities (e.g., in the same quintile), the treatment decision actually observed at the individual level can be regarded as independent of disease severity, apart from residual confounding.

Propensity score

The logistic model used the following variables to estimate the probability of being treated with methotrexate, leflunomide, sulfasalazine and/or anti-TNF drug within 6 months after first reported synovitis: Centre, age, 28-joint disease activity score (DAS28), sex, C-reactive protein (CRP) level, erosions present (yes/no), co-morbidity present (yes/no), rheumatoid factor present (yes/no), anti-CCP2 antibodies present (yes/no), time to visit a rheumatologist (<12 vs. >12 weeks), symmetric arthritis present (yes/no), involvement of hand joints (yes/no), and involvement of more than 3 joint groups (yes/no). Contributory variables were selected by stepwise forward selection, with p=0.3 as a limit for including a potential variable. Baseline was defined as the time point of first reported synovitis. To ascertain this, the patients were asked when they he had first noticed any swelling in a joint that was (according to the rheumatologist) currently swollen.

Hypotheses

The following hypotheses were tested: 1) an earlier treatment start –defined as <3 months from the time of arthritis onset, (i.e. first swollen joint)- would lead to less radiographic progression than a later DMARD start after adjustment for propensity scores; and 2) this gain would be gretaest in patients with more severe disease (quintiles with highest propensity scores).

Analysis and statistics

Radiographic progression in patients who were versus those who were not treated within the first 3 months was compared by Mann-Whitney U test. The effect of an early DMARD start on radiographic progression was evaluated using a generalized linear model in which change in 1-year Sharp-score was modeled by treatment start (early vs. late) as well as propensity score.

Patients were divided into propensity quintiles, based on their individual propensity scores. By definition, the rate of patients starting with a DMARD early should increase per quintile because of the physician's perception of increasing prognostic severity and disease activity. Subsequently, in an exploratory analysis radiographic progression was analysed per quintile according to

early DMARD start (yes vs. no). The limited number of patients per propensity quintile likely precludes a meaningful statistical comparison, so we refrained from statistically comparing within subgroups and report the results as a trend.

RESULTS

Patient characteristics.

Of the 813 included patients in ESPOIR cohort, 661 patients had complete data and were included in the analyses and the remaining 152 could not be analyzed. The main reason for exclusion of patients from analysis was missing radiographs at baseline (n=82) and/or at 1 year (n=141). Baseline characteristics in the group of 661 patients who were and the group who were excluded were similar (table 1).

Table 1. Baseline characteristics of included patients

Characteristic	Included in analysis (n=661)	Not included (n=152)
Age, mean ± SD years	48.6 (12.1)	45.7 (14.2)
Gender (female), n (%)	510 (77.2)	114 (75.0)
DAS28, mean ± SD	5.1 (1.3)	5.2 (1.4)
SHS, mean ± SD	5.8 (7.8)	N/A
CRP, mean ± SD mg/liter	9 (33.5)	19.4 (27.3)
Hand involvement, n (%)	624 (94.4)	132 (86.8)
RF positive, n (%)	294 (44.5)	48 (31.6)
Anti-CCP2 positive, n (%)	271 (41)	57 (37.5)
Fulfilled 2010 ACR/EULAR criteria for RA, n (%)	525 (79.4)	116 (76.3)
Fulfilled 1987ACR criteria for RA, n (%)	483 (73.1)	94 (61.8)

* DAS28 = 28-joint Disease Activity Score; SHS = Sharp/van der Heijde score; NA = not available; CRP = C-reactive protein; RF =rheumatoid factor; anti–CCP-2 = anti–cyclic citrullinated peptide 2; ACR = American College of Rheumatology; EULAR = European League Against Rheumatism.

Overall, 527/661 (79.7%) of the 661 analyzed patients were started on DMARD therapy within one year following symptom onset. Methotrexate was the most commonly prescribed first DMARD (63%), either as monotherapy (58%) or in combination with other DMARDs (hydroxychloroquine, sulfasalazine, leflunomide or TNF-blocking drugs (5%)). Sulfasalazine was chosen in 66 patients (13%), and leflunomide in 31 patients (6%). DMARDs not taken into account in our analysis (mainly hydroxychloroquine monotherapy) were prescribed in 90 patients.

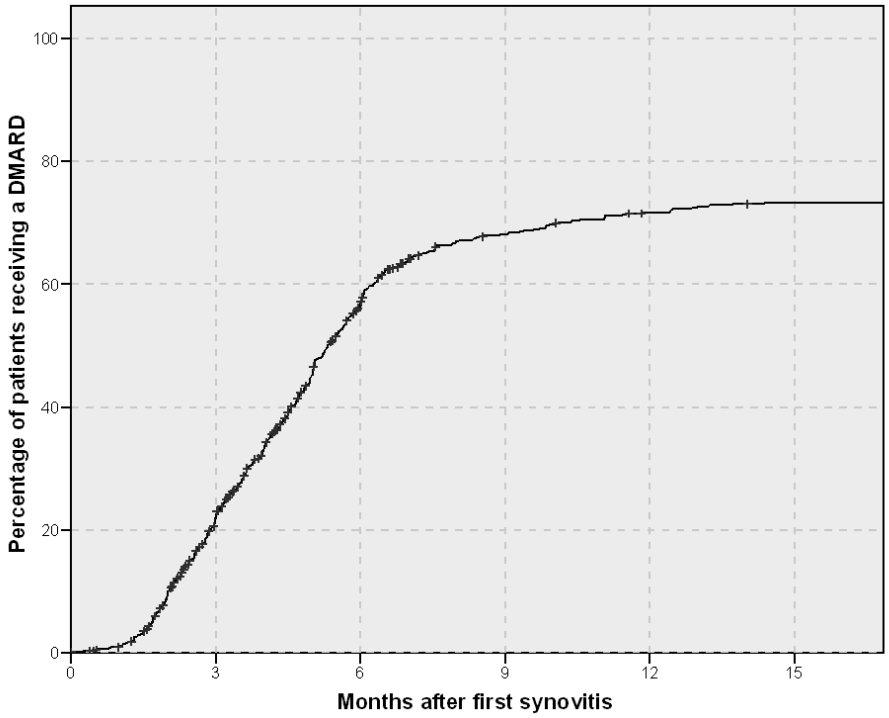

Figure 1. Percentage of patients starting disease-modifying antirheumatic drug (DMARD) treatment, by amount of time since the onset of synovitis.

Time-to-DMARD start was very heterogeneous, as shown in figure 1. The proportion of patients starting DMARD therapy increased rapidly over the first 6 months and leveled off thereafter. Twenty percent of the patients started DMARDs within 3 months of symptom onset, 55% started DMARDs > 3 months from the time of symptom onset, and 25% did not start DMARDs at all. Baseline characteristics of the patients who began treatment within 3 months and those who did not begin treatment within 3 months are reported in Table 2. An imbalance in the type of DMARD treatment used may theoretically have had an impact on radiographic progression. However, we did not identify such an imbalance. The somewhat higher frequency of TNF blockade treatment among patients starting DMARDs later may have worked against such a bias. Combination therapy was rarely chosen, which makes it unlikely that differences in the usage of combination therapy had an effect.

Radiographic progression

The mean ± SD total SHS at baseline was 5.8 ± 7.8 (range 0–56), with a median score of 3 and an interquartile range (IQR) of 1–7.5. The rather high baseline

Table 2. Baseline characteristics of patients treated/not treated within 3 months after first swollen joint.

	Treated within 3 months (n=140)	Not treated within 3 months (n=521)
Age, mean ± SD years	46.7 (12.6)	49.2 (11.9)
DAS28, mean ± SD	5.61 (1.18)	4.96 (1.30)
SHS, mean ± SD	4.7 (5.9)	6.1 (8.2)
CRP, mean ± SD mg/liter	26.9 (42)	18.8 (30.6)
RF positive, n (%)	73 (52.1%)	221 (42.4%)
Anti-CCP2 positive, n (%)	77 (55%)	194 (37.2%)
Fulfilled 2010 ACR/EULAR criteria for RA, n (%)	126 (90%)	399 (76.6%)

DAS28 = 28-joint Disease Activity Score; SHS = Sharp/van der Heijde score; CRP = C-reactive protein; RF =rheumatoid factor; anti–CCP-2 = anti–cyclic citrullinated peptide 2; ACR = American College of Rheumatology; EULAR = European League Against Rheumatism.

values in some patients appear surprising, but they are seen more frequently in cohorts of patients with short symptom duration. There may be several reasons for this: early subclinical joint inflammation that is not recognized by the patient, inaccurate symptom recall, and associated osteoarthritis that may cause damage resembling erosions and joint space narrowing in RA. The median radiographic progression at 1 year was 0 (IQR 0–1) and the mean ± SD change was 1.5 ± 4.3 units (range 0–36). Most patients (72%) did not show any radiographic progression over 1 year, but 8% had severe progression (>5 units). The erosion score at baseline was 2.8 ± 4.7 (range 0–40). Change in the erosion score at 1 year was observed in 179 patients (27.1%). The mean change in the erosion score was 1.2 ± 3.5 units (range 0–37). When patients were grouped according to whether they did or did not begin DMARD treatment within 3 months of symptom onset, the difference in crude mean radiographic progression was not significant (1.2 ± 3.4 units [range 0–19] in patients starting DMARDs within 3 months and 1.6 ± 4.5 units [range 0–37] in patients starting DMARDs later (p=0.37).

Intraclass correlation coefficients were >0.99 for both radiographic status scores and radiographic change scores. The smallest detectable change was calculated at 1.0 SHS unit.

Findings of the propensity analysis.

In the final logistic model, the investigation center, DAS28 score, time to first rheumatologist visit, RF positivity, involvement of >3 joint groups, CRP level, and anti-CCP antibody positivity remained as contributory factors (listed in decreasing order of contribution). Age, sex, presence of erosions, comorbidity,

symmetric arthritis, and involvement of hand joints were not contributory in the model. Subsequently, in order to investigate whether the perceived disease activity and severity were influencing the crude differences in radiographic progression rate, the propensity score was included as a covariate in the linear regression analysis. The estimated marginal means were 0.8 units (SE 0.37) in patients starting DMARDs within 3 months and 1.7 units (SE 0.19) in patients starting DMARDs later (p = 0.033), thus confirming the difference found in the crude analysis.

(SE is reported here because it is the estimation provided in a generalized linear model.) Subsequently, patients were divided into propensity quintiles (Figure 2). As expected, the proportion of patients starting DMARDs early increased by increasing quintile (increasing prognostic severity), although only 37.6% of patients in the highest quintile (worst prognosis) started DMARD treatment within 3 months of the onset of synovitis.

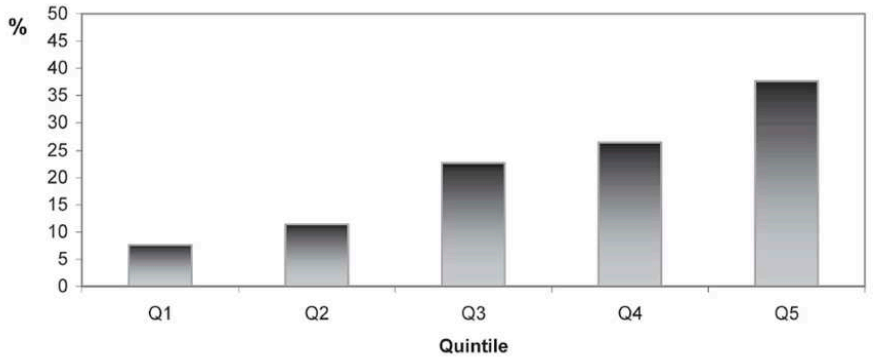

Figure 2. Percentage of patients starting disease-modifying antirheumatic drug treatment within 3 months of synovitis onset, by propensity score quintile (Q) (higher quintiles reflect greater disease severity).

Figure 3 shows probability plots of individual radiographic progression scores by DMARD treatment start (early versus delayed) in the individual quintiles. In the first 3 quintiles (better prognosis) there were no important differences in radiographic progression between those who started DMARDs within 3 months and those who started DMARDs beyond 3 months. A trend suggesting benefit of early treatment, especially in patients in the fourth and fifth quintiles (worse prognosis), was observed.

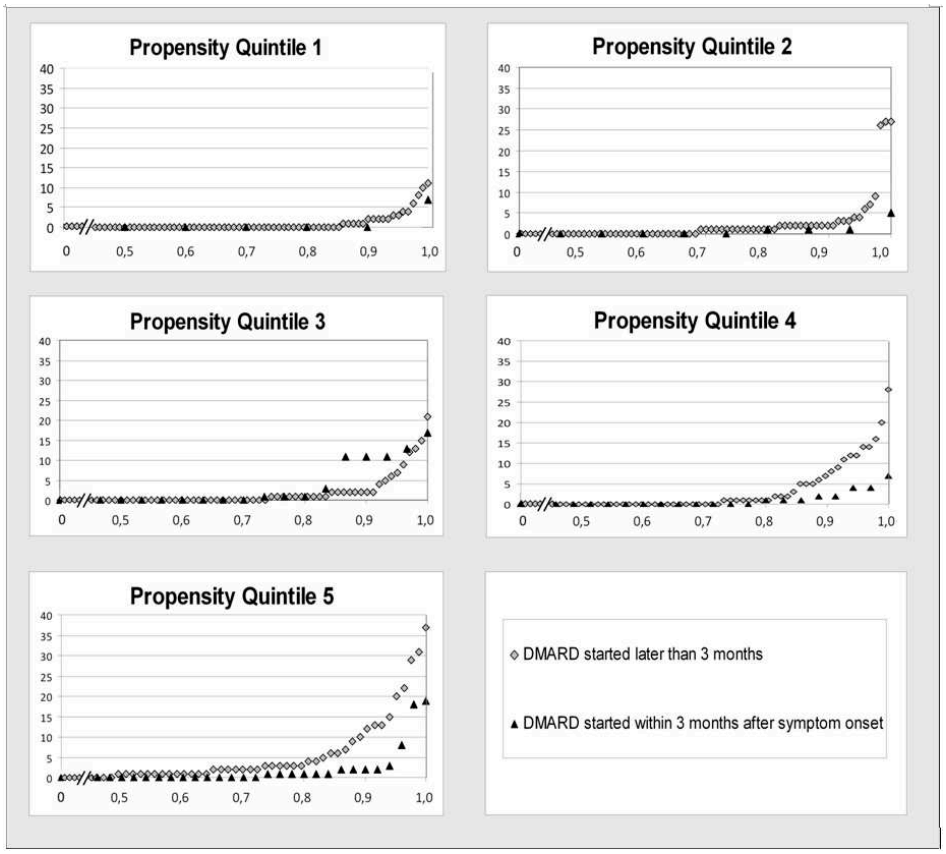

Figure 3. Probability plots of individual radiographic progression scores, by treatment category (disease-modifying antirheumatic drug [DMARD] treatment started within 3 months of synovitis onset [triangles] or not started within 3 months of synovitis onset [diamonds]) and by propensity score quintile.

Findings of sensitivity analysis.

Additional analyses, conducted in order to test the robustness and validity of the approach, yielded similar conclusions. The conclusions were unchanged when corticosteroid use was one of the factors included in the propensity model or when only specific DMARDs were used to define early treatment start. Taking as a minimum the use of at least 7.5 mg/day prednisone equivalent for .3 months in the first year of disease, the estimated marginal means for the change in radiographic progression score were similar to those obtained in the original propensity analysis (0.6 SHS units versus 1.8 SHS units in patients who did versus those who did not start DMARD treatment within 3 months; p=0.008). When the propensity score was based on the start of only methotrexate and/or anti-TNF within 6 months, radiographic progression was also lower in patients who had started treatment within 3 months versus those who

had started later (0.9 SHS units versus 1.6 SHS units), although the difference was not statistically significant (P=0.11). Other approaches to determining the propensity score (such as the inclusion of the baseline SHS score instead of the presence or absence of erosions) also resulted in similar conclusions.

DISCUSSION

The results of this study add to the sparse evidence that starting DMARD treatment very early in patients with inflammatory arthritis is favorable with regard to radiographic progression. A trend appears to suggest that especially patients with a relatively unfavorable prognosis benefit from early initiation of treatment. This observation must be interpreted with caution in view of the limited sample size and short follow up period in the present study. However, it is in accordance with observations stemming from post hoc analyses from clinical trials comparing intensive and less intensive treatment, which have shown that patients with the worst prognostic profile especially benefit from intensive treatment, while those with relatively mild disease do well with less intensive therapy (20,21). Our observations could be interpreted to suggest that the prognostic profile is important not only in the choice between intensive and less intensive treatment strategies, but also in the choice between a very early start and a delayed one. Unfortunately, the propensity score cannot be translated directly into prognostic variables.

Previous studies have also investigated the impact of early versus delayed treatment start in patients with early inflammatory arthritis. Lard et al prospectively followed up patients referred to an early arthritis clinic who first received symptomatic treatment and subsequently received sulfasalazine or hydroxychloroquine (13). They compared radiographic progression in these patients versus radiographic progression in patients starting DMARD therapy within 15 days after referral, and found that progression was significantly lower in the group that received early DMARD treatment. Such studies have led to a paradigm shift in the treatment strategy for RA, resulting in a recommendation of early aggressive treatment rather than a pyramid-like approach in which the initiation of effective DMARDs is postponed. Important limitations of such studies are that the drugs investigated did not include methotrexate (the current anchor drug in early RA), in the majority of patients the lag time between symptom onset and treatment initiation was beyond current recommendations, and different periods in history—covering different treatment paradigms—were compared.

Bukhari et al were the first to report on radiographic progression in an early arthritis cohort in which there was no formal treatment protocol (22). Using propensity modeling, they convincingly argued that radiographic progression at 5 years remained worse in patients for whom treatment had been delayed by >6 months. In their work, however, the propensity model was based on the start of any DMARD, including corticosteroids, over the entire 5-year follow up period and the probability of receiving treatment was evaluated based on data collected at baseline only, while clinical status does not necessarily remain stable over such a long time.

The strength of our approach is mainly that the propensity score we have designed includes a prognostic profile that is based both on data at first evaluation and on data during the first 6 months of follow up. Of note, the patients were closely monitored since they were included in the ESPOIR cohort, but treatment decisions were left entirely to the discretion of the local physician(s), and can thus be regarded as a reflection of current daily clinical practice.

One may expect that the observed differences in prognostic factors at first evaluation are an appropriate reflection of the heterogeneity rheumatologists encounter among patients referred with early inflammatory arthritis. The methodologic approach we have used enables comparisons of therapeutic interventions that could not be made under conditions of a clinical trial that does not incorporate judgments of severity but rather allocates patients irrespective of prognostic profile.

However, the propensity model also has limitations. There are several potentially important variables that were not assessed but might be taken into account by the rheumatologist during the clinical evaluation (intangible factors). Obviously, it is impossible to adjust for such unmeasured characteristics, and the possibility of residual and/or unmeasured confounding remains.

In conclusion, our study showed that patients with early inflammatory arthritis who began DMARD treatment early had improved radiographic outcome after adjustment for propensity score. These findings corroborate the recommendation of very early treatment initiation in patients with early inflammatory arthritis, in order to improve long-term prognosis.

REFERENCES

1. Combe B, Landewe R, Lukas C et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2007;66(1):34-45.
2. Emery P, Breedveld FC, Dougados M et al. Early referral recommendation for newly diagnosed rheumatoid arthritis: evidence based development of a clinical guide. Ann Rheum Dis. 2002;61(4):290-7.
3. Saag KG, Teng GG, Patkar NM et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum. 2008;59(6):762-84.
4. Smolen JS, Landewe R, Breedveld FC et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis.
5. Boers M, Verhoeven AC, Markusse HM et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet. 1997;350(9074):309-18.
6. Kuriya B, Arkema EV, Bykerk VP et al. Efficacy of initial methotrexate monotherapy versus combination therapy with a biological agent in early rheumatoid arthritis: a meta-analysis of clinical and radiographic remission. Ann Rheum Dis.
7. Landewe RB, Boers M, Verhoeven AC et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum. 2002;46(2):347-56.
8. Mottonen T, Hannonen P, Leirisalo-Repo M et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet. 1999;353(9164):1568-73.
9. Egsmose C, Lund B, Borg G et al. Patients with rheumatoid arthritis benefit from early 2nd line therapy: 5 year followup of a prospective double blind placebo controlled study. J Rheumatol. 1995;22(12):2208-13.
10. Nell VP, Machold KP, Eberl G et al. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. Rheumatology (Oxford). 2004;43(7):906-14.
11. van der Heide A, Jacobs JW, Bijlsma JW et al. The effectiveness of early treatment with "second-line" antirheumatic drugs. A randomized, controlled trial. Ann Intern Med. 1996;124(8):699-707.
12. Finckh A, Liang MH, van Herckenrode CM et al. Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: A meta-analysis. Arthritis Rheum. 2006;55(6):864-72.
13. Lard LR, Visser H, Speyer I et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med. 2001;111(6):446-51.
14. Combe B. The French early arthritis registry. Clin Exp Rheumatol. 2003;21(5 Suppl 31):S123-8.
15. Combe B, Benessiano J, Berenbaum F et al. The ESPOIR cohort: A ten-year follow-up of early arthritis in France. Methodology and baseline characteristics of the 813 included patients Joint Bone Spine. 2007;74(5);440-5. Epub 2007 Jul 26.
16. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol. 2000;27(1):261-3.

17. Bruynesten K, Boers M, Kostense P et al. Deciding on progression of joint damage in paired films of individual patients: smallest detectable difference or change. Ann Rheum Dis. 2005;64(2):179-82.
18. Little RJ, Rubin DB. Causal effects in clinical and epidemiological studies via potential outcomes: concepts and analytical approaches. Annual review of public health. 2000;21:121-45.
19. Smolen J, Van der Heijde D, St Clair EW et al. Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab: results from the ASPIRE trial. Arthritis Rheum. 2006;54(3):702-10.
20. Verschueren P, Esselens G, Westhovens R. Daily Practice Effectiveness of a Step Down Treatment in comparison to a Tight Step Up for Early Rheumatoid Arthritis. Rheumatology (Oxford). 2007;47:53-8.
22. Bukhari MA, Wiles NJ, Lunt M et al . Influence of disease-modifying therapy on radiographic outcome in inflammatory polyarthritis at five years: results from a large observational inception study. Arthritis and rheumatism. 2003;48(1):46-53.